Contact us on Twitter:
@Pathology438

Important in Red.
Doctor's notes in Green

You will find out in the link below if any correction or notes unmentioned in the team's work were to be added. Please check it Frequently.
The editing file for the final's lectures

From :Lec 11 To Lec 15

Neoplasia

Neoplasm

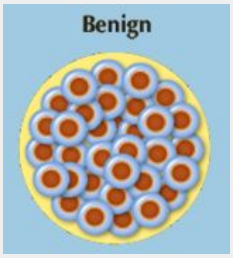
Definitions

Neoplasia: literally means “new growth.” A neoplasm often is referred to as a tumor, and the study of tumors is called oncology (from oncos, “tumor,” and logos, “study of”).

The division of neoplasms into benign and malignant categories is based on their potential clinical behavior.

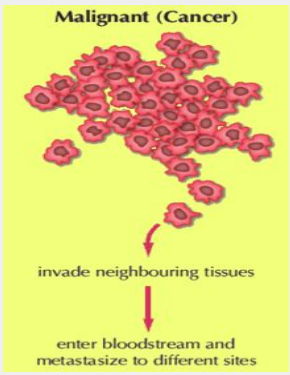
Classification of Tumors:

Benign(حميد): the microscopic and gross characteristics of the lesion are considered to be relatively innocent.



- Tumors remain localized (well-circumscribed).
- Tumors are amenable (responsive) to local surgical removal.
- Patients generally survive.

Malignant: lesions can invade (cell membrane base) and destroy adjacent structures and spread to distant sites (metastasize) to cause death.



- Usually not capsulated.
- Has the ability to spread.
- Hard to treat and remove.
- invades\destructs the surrounding structure.
- Not well-circumscribed.

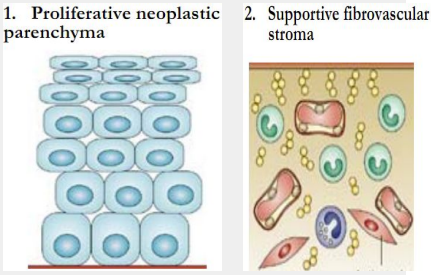
All tumors, benign and malignant, have two basic components:

1. **The parenchyma**, made up of transformed or neoplastic cells.

2. **The supporting stroma**, host-derived, non-neoplastic stroma, made up of connective tissue, blood vessels, and host-derived inflammatory Cells. (important for growth)

Nomenclature of Tumors

The nomenclature of tumors and their biologic behavior are based primarily on the parenchymal component.
However, the growth and evolution of tumors is critically dependent on their stroma as an adequate stromal blood supply is a requisite for the tumor cells to live and divide.



Benign tumors are designated by attaching the suffix -oma to the cell type from which the tumor arises.

The nomenclature of **mesenchymal tumors** usually apply this rule:
- Benign tumor arising in fibrous tissue: Fibro + oma = Fibroma.
- Benign tumor arising in fatty tissue: Lipo + oma = lipoma.
- Benign tumor arising in cartilage: chondro + oma = chondroma.
- Benign tumor arising in skeletal muscle: Rhabdomyo + oma = rhabdomyoma.
- Benign tumor arising in smooth muscle: Leiomyo + oma = leiomyoma.
- Benign tumor arising in bone tissue: Oste + oma = Osteoma.

Exceptions!!
Some glaring inconsistencies may be noted. For example the terms: are used for malignant tumors.

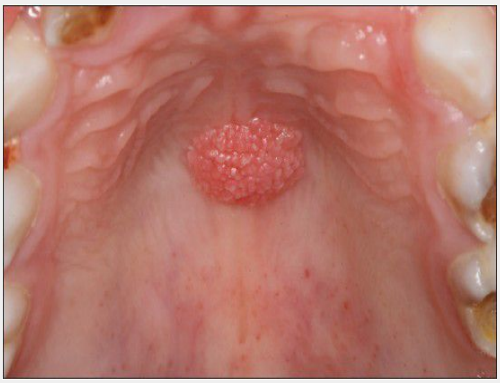
- **Melanoma** (from the melanocytes of the skin).
- **Mesothelioma** (from the peritoneal cavity…mesothelium).
- **Seminoma** (from the testis).
- **Lymphoma** (from lymphoid tissue).

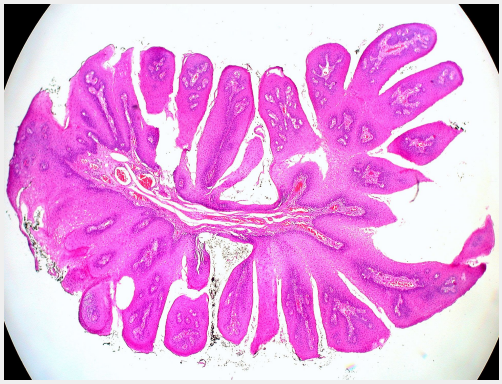
The nomenclature of benign epithelial tumors is more complex: cell of origin, microscopic pattern or macroscopic appearance.

Adenoma: is generally applied to **benign epithelial neoplasms** producing gland patterns and to neoplasms derived from glands but not necessarily exhibiting glandular patterns.

Nomenclature of Tumors - Benign

Papillomas: Benign epithelial neoplasms producing microscopically or macroscopically visible finger-like (projections) or warty projections from epithelial surfaces.

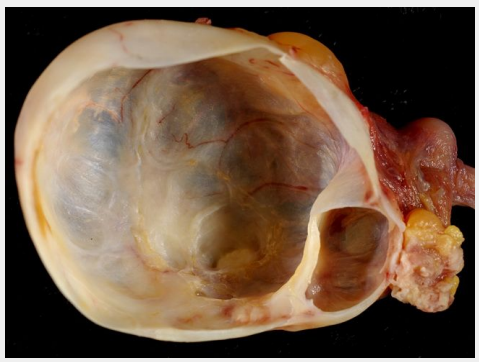




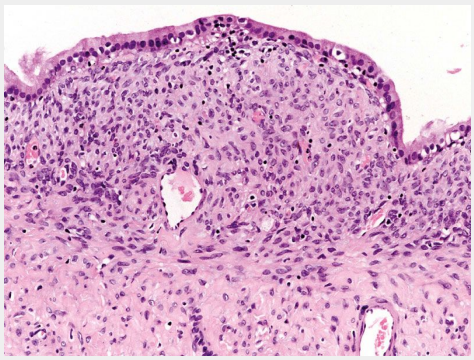
Cystadenomas: Benign epithelial neoplasms forming large cystic masses (bag like), as in the **ovary** (very common there).

Some of the latter produce papillary patterns that protrude into cystic spaces and are called **papillary cystadenomas.** (combining both type "more complicated")

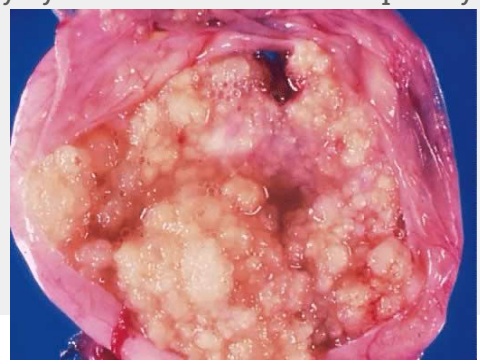
Cystadenoma – Macroscopically



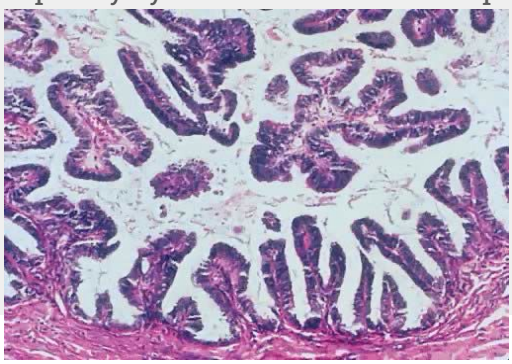
Cystadenoma – Microscopically



Papillary cystadenoma – Macroscopically

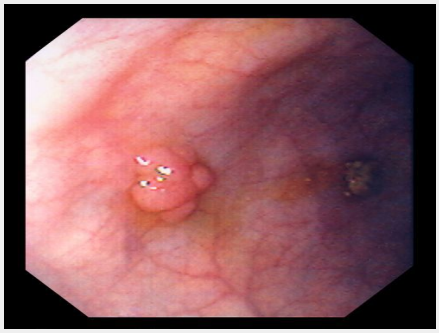


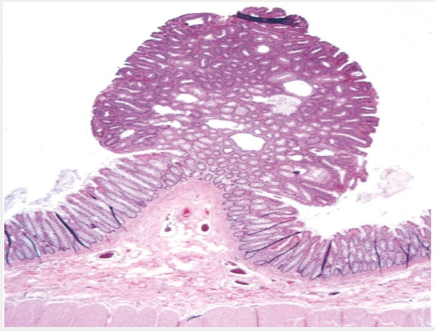
Papillary cystadenoma – Microscopically



Nomenclature of Tumors - Benign

Polyp: is a mass that projects above a mucosal surface, as in the gut(from the mouth till the anus), to form a macroscopically visible structure. (it is not tumor)





Nomenclature of Tumors - Malignant

Sarcomas: Malignant neoplasms arising in mesenchymal tissue.

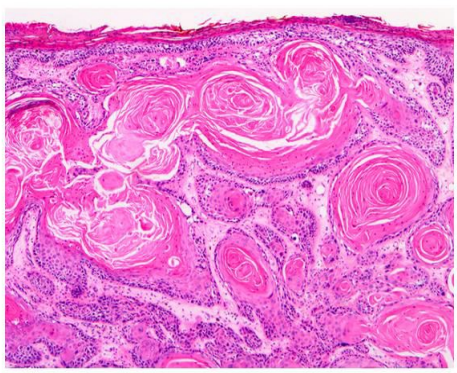
- Fibrosarcoma: a malignant tumor arising in fibrous tissue.
- Chondrosarcoma: a malignant tumor arising in cartilaginous tissue.
- Osteosarcoma: a malignant tumor arising in bone tissue.

Carcinoma(cancer): Malignant neoplasms arising from epithelial cells.

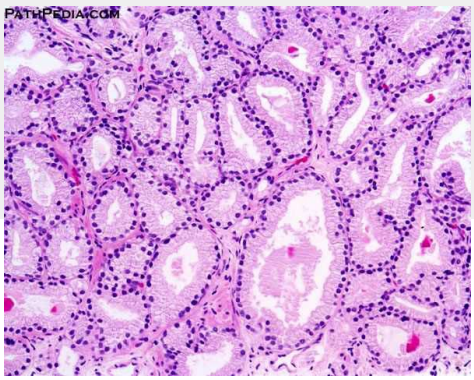
Carcinomas include:

- Carcinomas that arise from glandular epithelial cells (with or without forming glands): adenocarcinomas.
- Carcinomas that arise from squamous cells (some producing keratin): squamous cell carcinomas.
- Carcinomas that show little or no differentiation: poorly differentiated or undifferentiated carcinoma.

Squamous cell carcinoma

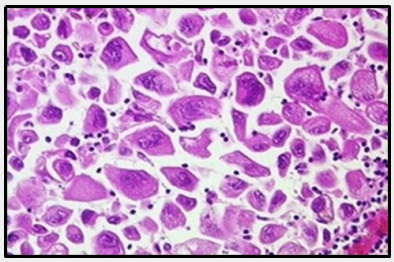


Adenocarcinoma



Nomenclature of Tumors - Malignant

Not infrequently, however, a cancer is composed of undifferentiated cells of unknown tissue origin,and must be designated merely as an **undifferentiated malignant tumor.**

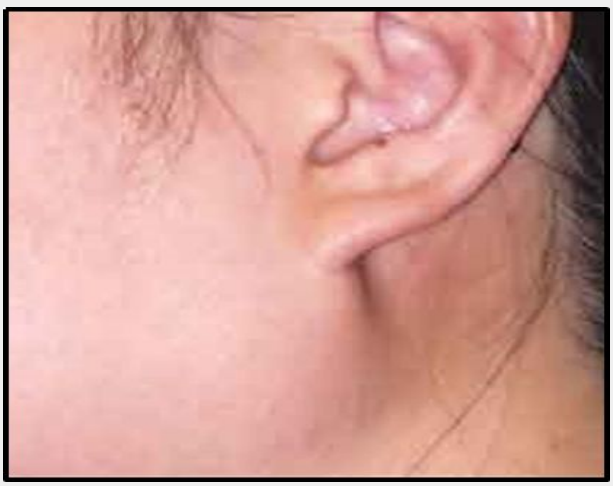


The transformed cells in a neoplasm, whether benign or malignant, often resemble each other, as though all had been derived from **a single progenitor**, consistent with t**he monoclonal origin of tumors**. (All tumor cells are similar to each other)(tumor arise from one cell "gone crazy")
In some unusual instances, however, divergent differentiation of a single neoplastic clone along **two lineages occurs**, creating the so-called mixed tumors.

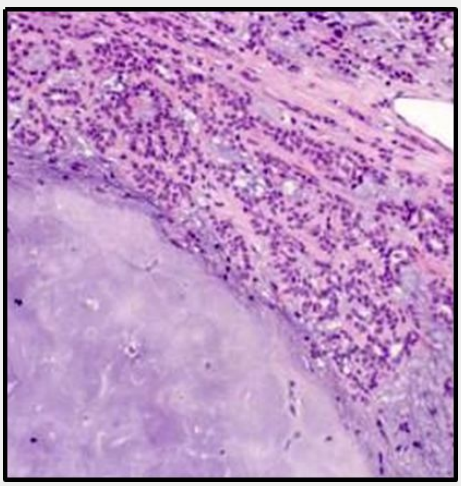
The best example is the mixed tumor of the salivary gland. These tumors have obvious epithelial components dispersed throughout a fibromyxoid (mucousy fiber) stroma, sometimes harboring islands of cartilage or bone.

All of these diverse elements are thought to derive from a single clone capable of giving rise to epithelial cells or myoepithelial cells, or both, and the preferred designation for these neoplasms is pleomorphic adenoma.
Pleomorphic adenoma حميد متعدد الأشكال : is a mixed tumor has the ability to produce two types of cells:
1- epithelium
2- myoepithelium : has properties of smooth muscle.

Macroscopically



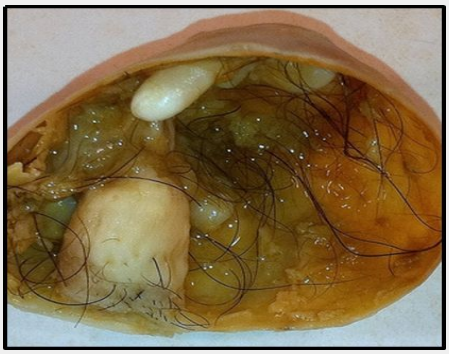
Microscopically



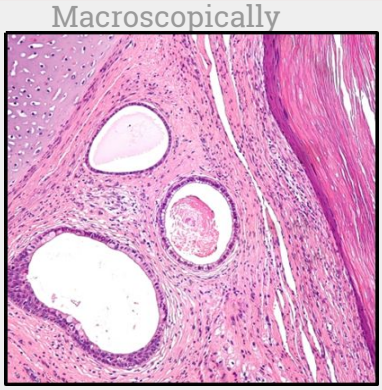
Teratoma

Teratoma is a special type of mixed tumor that contains recognizable mature or immature cells or tissues representative of more than one germ cell layer and sometimes all three. (trilaminar disc)
Teratoma originates from totipotential cells such as those normally present in the ovary and testis and sometimes abnormally present in sequestered midline embryonic rests. Such cells have the capacity to differentiate into any cell type found in the adult body.
Teratoma: has the ability to give any type of cell or tissue.
more abnormalities mean more faster to grow poorly differentiated.
"Mixed is not teratoma"
When all the components within the teratoma are well differentiated,
It is a benign (mature) teratoma.
when they are less differentiated, it is an immature, potentially or overtly,
malignant teratoma.

Macroscopically



Macroscopically



Hamartoma

Hamartoma is a mass of disorganized benign-looking tissue indigenous to the particular site.

pulmonary chondroid hamartoma, which contains islands of disorganized, but histologically normal smooth muscles, cartilage, bronchi, and vessels, epithelium.
Hamartomas have traditionally been considered developmental malformations, but some genetic studies have shown the presence of acquired translocations, suggesting a neoplastic origin.
(normal tissue and in the right place but disorganized)

Choristoma

Choristoma is a congenital anomaly consisting of a heterotopic rest of cells. (normal histological structure, normal funtional tissue but is in abnormal "wrong" location)

a small nodule of well-developed and normally organized pancreatic tissue may be found in the submucosa of the stomach, duodenum, or small intestine. Choristoma has usual trivial significance (Developmental annomiles)

Tissue of Origin	Benign	Malignant
One Parenchymal Cell Type		
Connective tissue and derivatives	Fibroma Lipoma Chondroma Osteoma	Fibrosarcoma Liposarcoma Chondrosarcoma Osteogenic sarcoma
Endothelium and related cell types		
Blood vessels	Hemangioma	Angiosarcoma
Lymph vessels	Lymphangioma	Lymphangiosarcoma
Mesothelium		Mesothelioma
Brain coverings	Meningioma	Invasive meningioma
Blood cells and related cell types		
Hematopoietic cells		Leukemias
Lymphoid tissue		Lymphomas
Muscle		
Smooth	Leiomyoma	Leiomyosarcoma
Striated	Rhabdomyoma	Rhabdomyosarcoma
Skin		
Stratified squamous	Squamous cell papilloma	Squamous cell or epidermoid carcinoma
Basal cells of skin or adnexa		Basal cell carcinoma
Tumors of melanocytes	Nevus	Malignant melanoma
Epithelial lining of glands or ducts	Adenoma Papilloma Cystadenoma	Adenocarcinoma Papillary carcinomas Cystadenocarcinoma
Lung	Bronchial adenoma	Bronchogenic carcinoma
Kidney	Renal tubular adenoma	Renal cell carcinoma
Liver	Liver cell adenoma	Hepatocellular carcinoma
Bladder	Urothelial papilloma	Urothelial carcinoma
Placenta	Hydatidiform mole	Choriocarcinoma
Testicle		Seminoma Embryonal carcinoma
More Than One Neoplastic Cell Type—Mixed Tumors, Usually Derived From One Germ Cell Layer		
Salivary glands	Pleomorphic adenoma (mixed tumor of salivary gland)	Malignant mixed tumor of salivary gland
Renal anlage		Wilms tumor
More Than One Neoplastic Cell Type Derived From More Than One Germ Cell Layer—Teratogenous		
Totipotential cells in gonads or in embryonic rests	Mature teratoma, dermoid cyst	Immature teratoma, teratocarcinoma

Differentiation & Anaplasia

Features to distinguish between benign & malignant tumors:

- **Differentiation & anaplasia**
- **Rate of growth**
- **Local invasion**
- **Metastasis**

Differentiation & anaplasia are characteristics seen only in the parenchymal cells that constitute the transformed elements of neoplasms.
Differentiation: the extent to which the parenchymal cells of the tumor resemble their normal counterparts morphologically and functionally.

- Well differentiated (the only bening)
- Moderately differentiated
- Poorly differentiated
- Undifferentiated (Anaplasia)

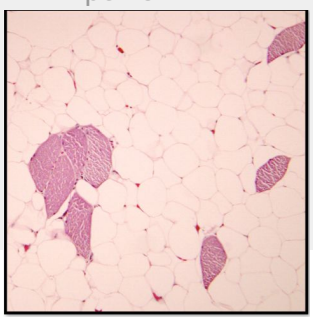
Benign neoplasms are composed of well-differentiated cells that closely resemble their normal counterparts.

• Lipoma: mature fat cells laden with cytoplasmic lipid vacuoles.
• Chondroma: mature cartilage cells that synthesize their usual cartilaginous matrix (evidence of morphologic and functional differentiation).
In well-differentiated benign tumors, mitoses are usually rare and are of normal configuration. benign neoplasms and even well-differentiated cancers of endocrine glands frequently elaborate the hormones characteristic of their origin.

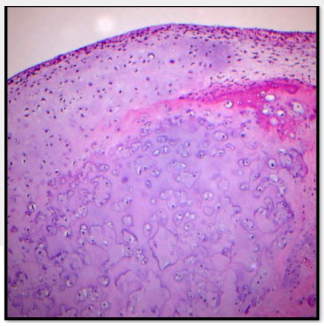
The stroma carrying the blood supply is crucial to the growth of tumors but does not aid in the separation of benign from malignant ones. the amount of stromal connective tissue determines the consistency of a neoplasm.

certain cancers induce a dense, abundant fibrous stroma (desmoplasia) , making them hard, so-called scirrhous tumors.

Lipoma



Chondroma

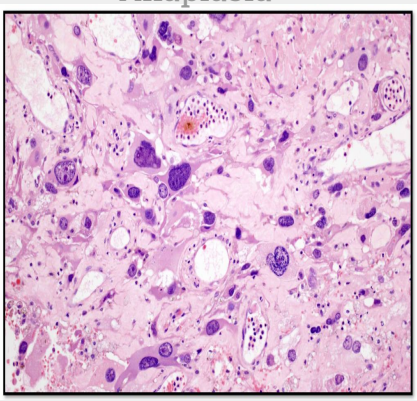


Differentiation & Anaplasia

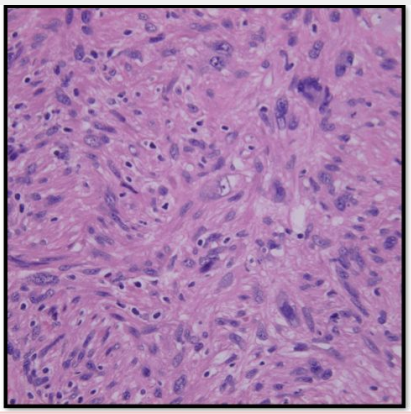
Malignant neoplasms are characterized by a wide range of parenchymal cell differentiation: from well differentiated to completely undifferentiated. Between the two extremes lie tumors loosely referred to as moderately differentiated.

Malignant neoplasms that are composed of undifferentiated cells are said to be anaplastic which means loss of the structural and functional differentiation. It is a hallmark of malignancy.

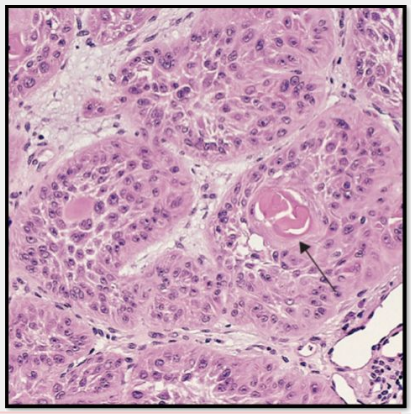
Anaplasia



leiomyosarcoma



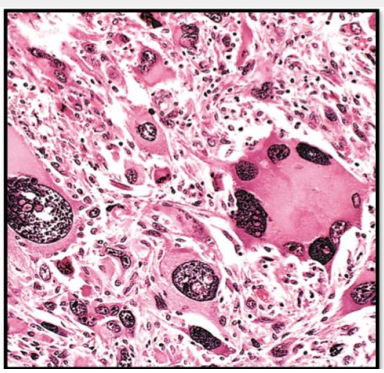
Squamous Cell carcinoma



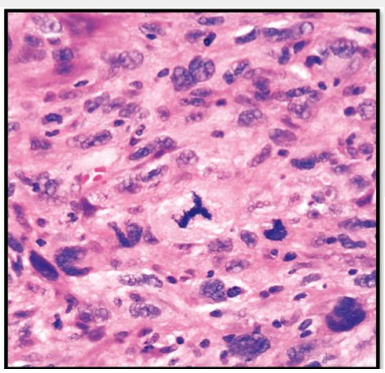
It is important to recognize the following histopathological features in any neoplasm:

- Pleomorphism: variation in size and shape
- Enlarged nuclei resulting in an increase of nuclear to cytoplasm ratio (that may approach 1:1 instead of the normal 1:4 or 1:6)
- Hyperchromasia (dark nuclei) due to coarse & clumped chromatin
- Prominent nucleoli
- Mitoses (typical or atypical forms)
- Giant cells: larger than their neighbors & possess either one enormous nucleus or several nuclei.

Tumor Giant Cell



Atypical Mitosis



Dysplasia

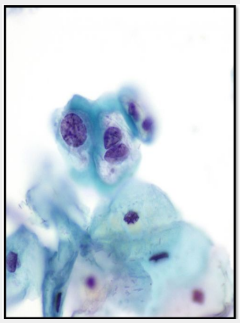
Dysplasia is a loss in the uniformity of the individual cells and a loss in their architectural orientation. It is a non-neoplastic process but a premalignant condition. It occurs mainly in the epithelia.

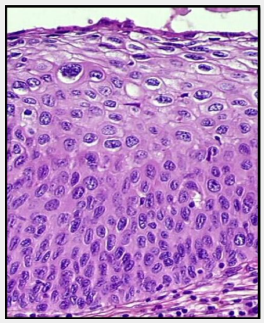
Dysplastic cells show a degree of: pleomorphism, ↑ N:C ratio, Hyperchromasia, irregular nuclei, increased mitoses, loss of polarity & a disordered maturation or total failure of maturation. (N= Nucleus C= cytoplasm)

Dysplasia does not mean cancer, and does not necessarily progress to cancer, it may be reversible.

The risk of invasive cancer varies with:
- grade of dysplasia (mild, moderate, severe)
- duration of dysplasia
- site of dysplasia

Differences between dysplasia & cancer:
- Lack of invasiveness.
- Reversibility

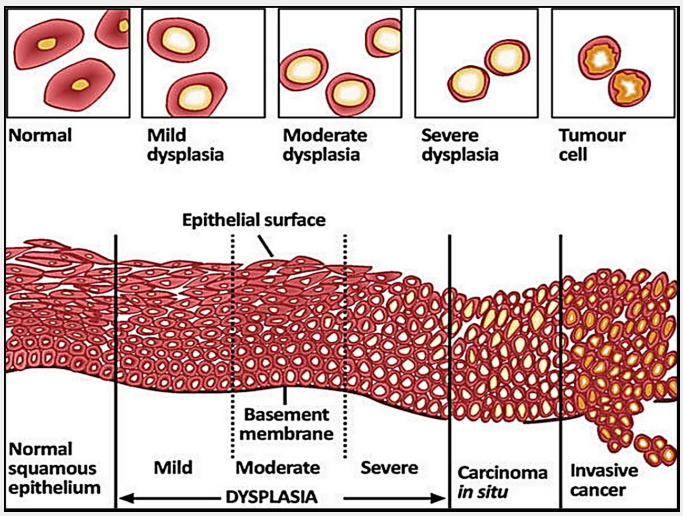


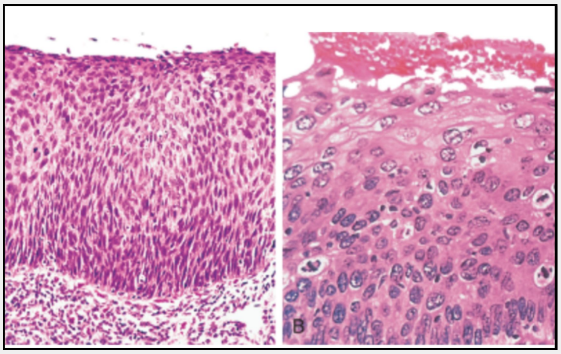


Carcinoma in Situ

If dysplastic changes involve the entire thickness of the epithelium it is called: **carcinoma in-situ** an intraepithelial malignancy in which malignant cells involve the entire thickness of the epithelium without penetration of the basement membrane.

It is applicable only to epithelial neoplasms, It is a true neoplasm with all of the features of malignant neoplasm except invasiveness, It displays the cytological features of malignancy without invading the basement membrane.





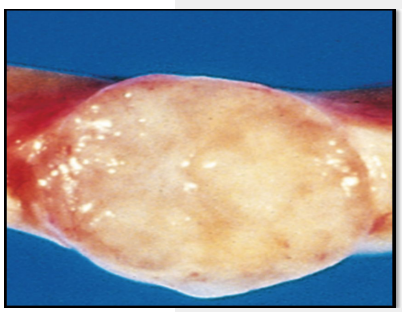
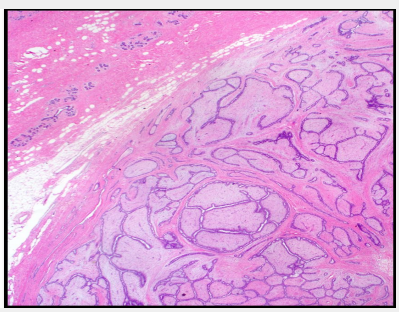
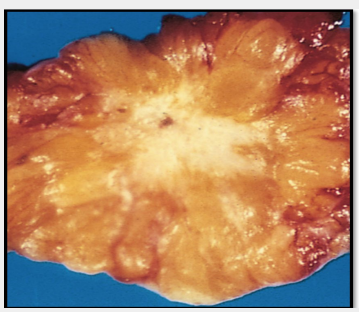
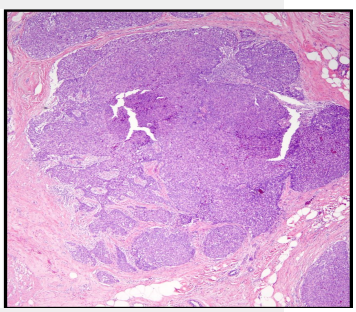
Rate of Growth

Benign tumors they usually grow slowly. Their growth is affected by: adequate blood supply, location or hormones e.g. leiomyoma of the uterus.

- They remain localized.
- They cannot invade.
- They are usually encapsulated

Malignant tumors They usually grow fast, the rate of growth of malignant tumors usually correlates inversely with their level of differentiation.Malignant tumors usually infiltrative (irregular)

- They invade the underlying basement membrane or stroma.
- They are destructive.
- They are usually not encapsulated.

Metastasis

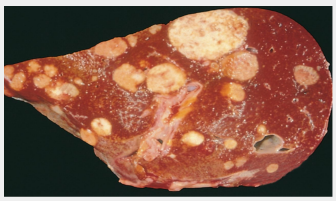
it is the development of secondary implants of a tumor that are discontinuous with the primary tumor & located in remote tissues. More than any other attribute, the property of metastasis identifies a neoplasm as malignant. (the most important sign of malignancy)

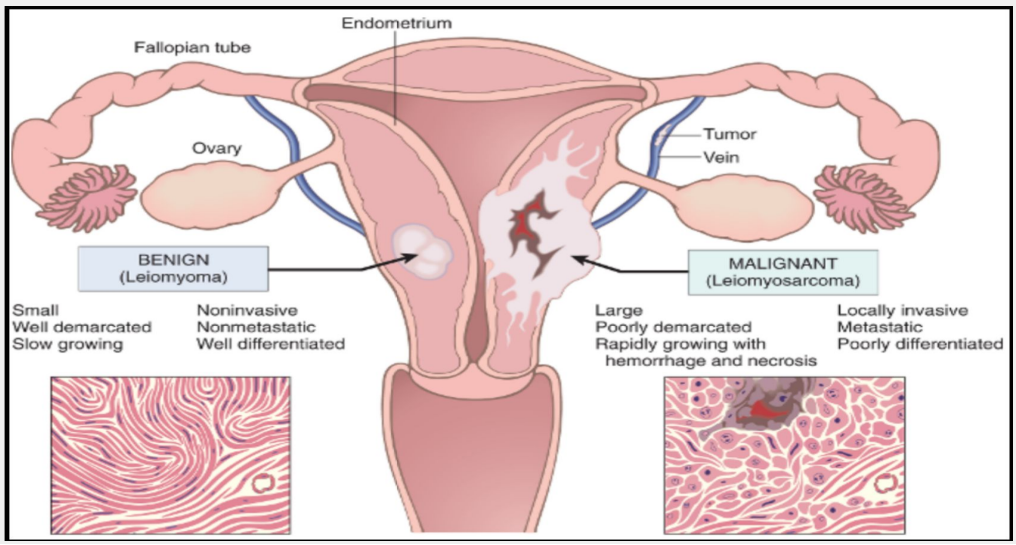
Cancer have different ability to metastasize. Approximately 30% patients present with clinically evident metastases. Generally, the more anaplastic and the larger the primary tumor, the more likely it metastasizes.

Malignant neoplasms disseminate by one of three pathways:

- seeding within body cavities occurs when neoplasms invade a natural body cavity. This mode of dissemination is particularly characteristic of cancers of the ovary, which often cover the peritoneal surfaces widely.
- lymphatic spread is more typical of carcinomas.
  - Breast carcinoma → axillary lymph node
  - Lung carcinomas → bronchial lymph nodes
- hematogenous spread (the blood vessels) is favored by sarcomas but can also occur in carcinomas. Veins are more commonly invaded.

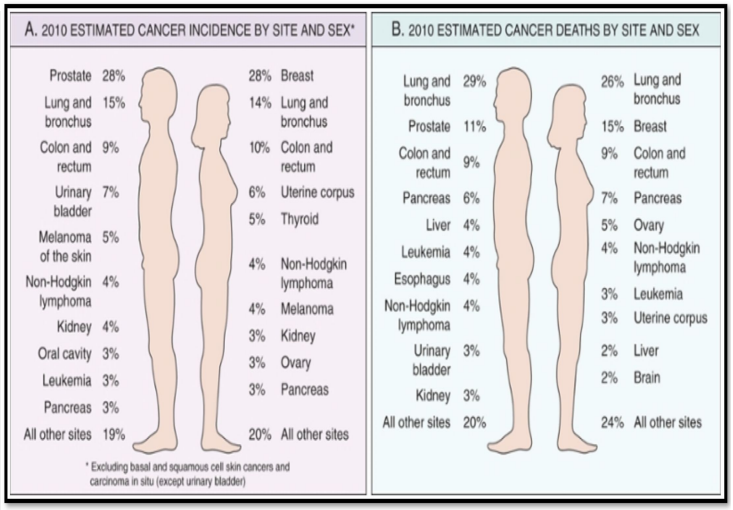
The liver and lungs are the most frequently involved secondary sites.





Cancer Incidence

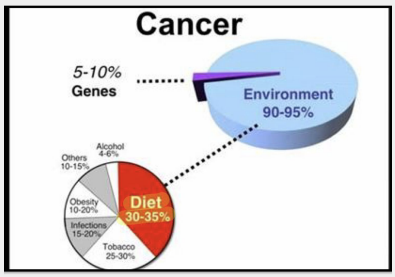
Cancer Incidence:
The most common cancer in lung cancer for both genders.
The second is prostate cancer to male and breast cancer to female.
The thirds is colon cancer for both genders.



Geographic and environmental factors → Age → Hereditary factors → Acquired preneoplastic conditions

Geographic & environmental factors:

- Exposure to asbestos ⟶ mesothelioma
- Smoking ⟶ lung cancer
- Multiple sexual partners ⟶ cervical carcinoma
- fat-rich diet ⟶ colon carcinoma



Agents or Groups of Agents	Human Cancers for Which Reasonable Evidence Is Available	Typical Use or Occurrence
Arsenic and arsenic compounds	Lung carcinoma, skin carcinoma	By-product of metal smelting; component of alloys, electrical and semiconductor devices, medications and herbicides, fungicides, and animal dips
Asbestos	Lung, esophageal, gastric, and colon carcinoma; mesothelioma	Formerly used for many applications because of fire, heat, and friction resistance; still found in existing construction as well as fire-resistant textiles, friction materials (i.e., brake linings), underlayment and roofing papers, and floor tiles
Benzene	Acute myeloid leukemia	Principal component of light oil; despite known risk, many applications exist in printing and lithography, paint, rubber, dry cleaning, adhesives and coatings, and detergents; formerly widely used as solvent and fumigant
Beryllium and beryllium compounds	Lung carcinoma	Missile fuel and space vehicles; hardener for lightweight metal alloys, particularly in aerospace applications and nuclear reactors
Cadmium and cadmium compounds	Prostate carcinoma	Uses include yellow pigments and phosphors; found in solders; used in batteries and as alloy and in metal platings and coatings
Chromium compounds	Lung carcinoma	Component of metal alloys, paints, pigments, and preservatives
Nickel compounds	Lung and oropharyngeal carcinoma	Nickel plating; component of ferrous alloys, ceramics, and batteries; by-product of stainless-steel arc welding
Radon and its decay products	Lung carcinoma	From decay of minerals containing uranium; potentially serious hazard in quarries and underground mines
Vinyl chloride	Hepatic angiosarcoma	Refrigerant; monomer for vinyl polymers; adhesive for plastics; formerly inert aerosol propellant in pressurized containers

Cancer Incidence

Age: Generally, the frequency of cancer increases with age. Most cancer mortality occurs between 55 and 75 years of age and it also increases during childhood

The most common malignant tumors in children are:

- Leukemia
- CNS tumors
- Lymphomas
- Soft tissue & bone sarcomas

Hereditary factors:

- **Autosomal dominant cancer syndromes** Several well-defined cancers in which inheritance of a single mutant gene greatly increases the risk of developing a tumor.

- retinoblastoma in children

  40% of retinoblastoma are familial in nature.

  Carriers of this mutation have 10000 fold increase in the risk of developing retinoblastoma

- multiple endocrine neoplasia (MEN) syndrome
-

- **Autosomal recessive syndromes of defective DNA repair.** A group of rare autosomal recessive disorders is collectively characterized by chromosomal or DNA inability and high rates of certain cancers

  xeroderma pigmentosum

- **Familial cancers of uncertain inheritance:** All the common types of cancers that occur sporadically have been reported to occur in familial forms where the patterns of inheritance is unclear.

  E.g. breast, colon, ovary, brain

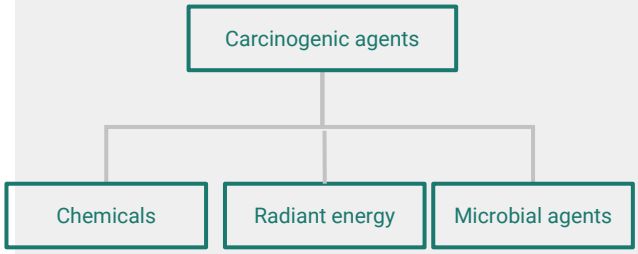
  Familial cancers usually have unique features:

- They start at early age
- They are multiple or bilateral (for ex: if it was a breast cancer it will be found in the two breasts)
- They occur in two or more relatives

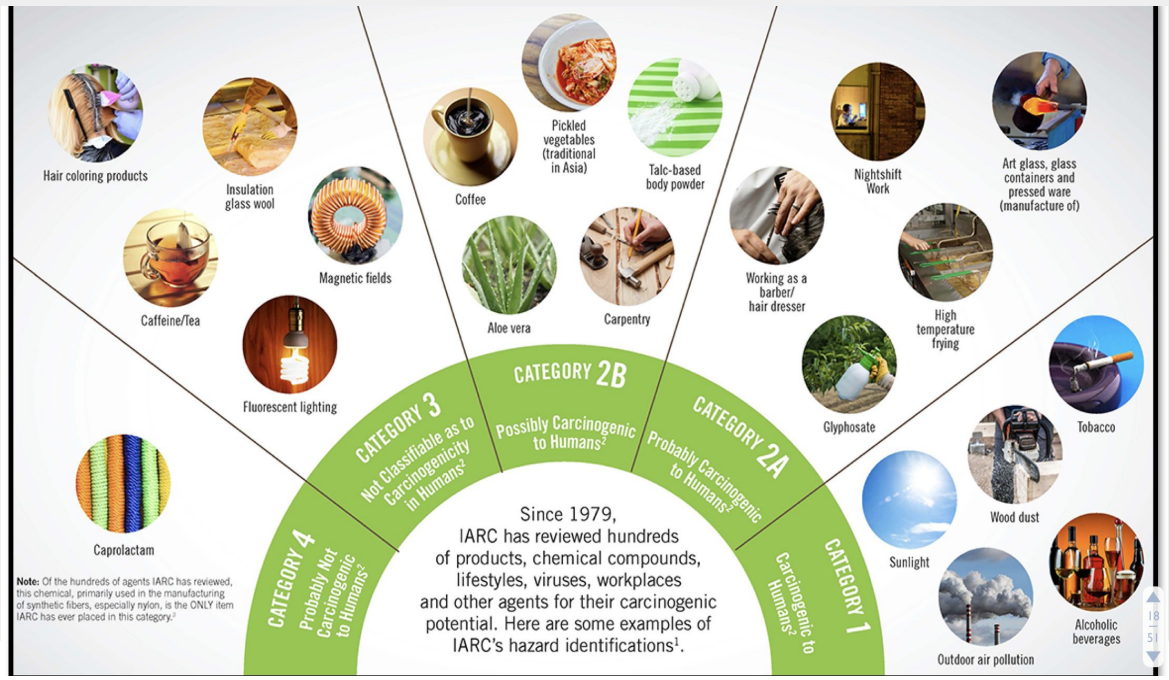
Cancer Incidence

Acquired pre-neoplastic conditions (predispose to cancer):

- Dysplastic bronchial mucosa in smokers ⟶ lung carcinoma
- Liver cirrhosis ⟶ liver cell carcinoma
- Margins of chronic skin fistulae ⟶ squamous cell carcinoma
- Endometrial hyperplasia ⟶ endometrial carcinoma
- Leukoplakia of the oral cavity, vulva or penis ⟶ squamous cell carcinoma
- Villous adenoma of the colon or rectum ⟶ colorectal adenocarcinoma



Inherited Predisposition	Gene(s)
Autosomal Dominant Cancer Syndromes	
Retinoblastoma	*RB*
Li-Fraumeni syndrome (various tumors)	*TP53*
Melanoma	*CDKN2A*
Familial adenomatous polyposis/colon cancer	*APC*
Neurofibromatosis 1 and 2	*NF1, NF2*
Breast and ovarian tumors	*BRCA1, BRCA2*
Multiple endocrine neoplasia 1 and 2	*MEN1, RET*
Hereditary nonpolyposis colon cancer	*MSH2, MLH1, MSH6*
Nevoid basal cell carcinoma syndrome	*PTCH1*
Autosomal Recessive Syndromes of Defective DNA Repair	
Xeroderma pigmentosum	Diverse genes involved in nucleotide excision repair
Ataxia-telangiectasia	*ATM*
Bloom syndrome	*BLM*
Fanconi anemia	Diverse genes involved in repair of DNA cross-links



Chemical Carcinogens

Chemical carcinogens can be natural or synthetic.

They can cause cellular damage via:

- Direct

  They require no metabolic conversion to become carcinogenic.

  They are in general weak carcinogens but are important because some of them are cancer chemotherapy drugs

  e.g. alkylating agents

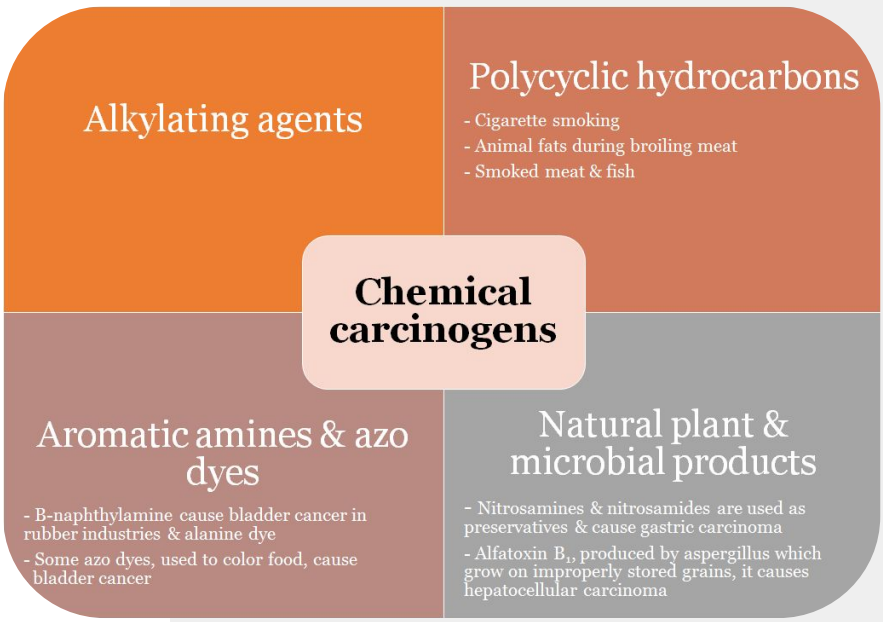
- Indirect

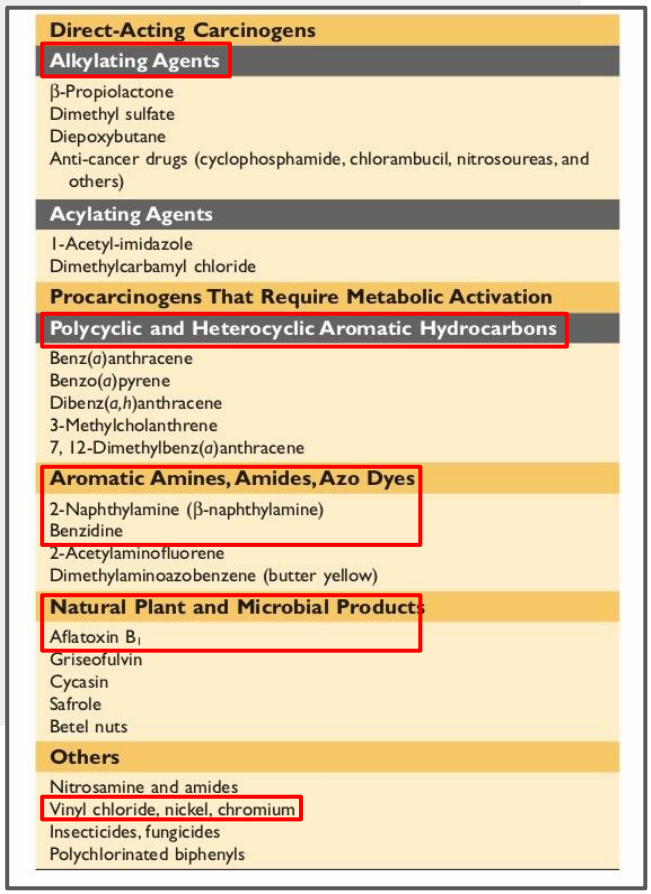
  They require metabolic conversion of the chemical compound (procarcinogen) to active & carcinogenic products (ultimate carcinogen).

  e.g. benzo[a]pyrene, aromatic amines, azo dyes & Aflatoxin B1

Mechanism of the action:
Most chemical carcinogens are mutagenic (cause genetic mutations).
The commonly mutated oncogenes & tumor suppressors are RAS and TP53.

All direct chemical carcinogens & ultimate chemical carcinogens are highly reactive as they have electron-deficient atoms. They react with the electron rich atoms in RNA, DNA & other cellular proteins.





Radiation

Radiation, whatever its source (UV rays of sunlight, x-rays, nuclear fission, radionuclides) is an established carcinogen. Radiation has mutagenic effects: chromosomes breakage, translocations and point mutations.

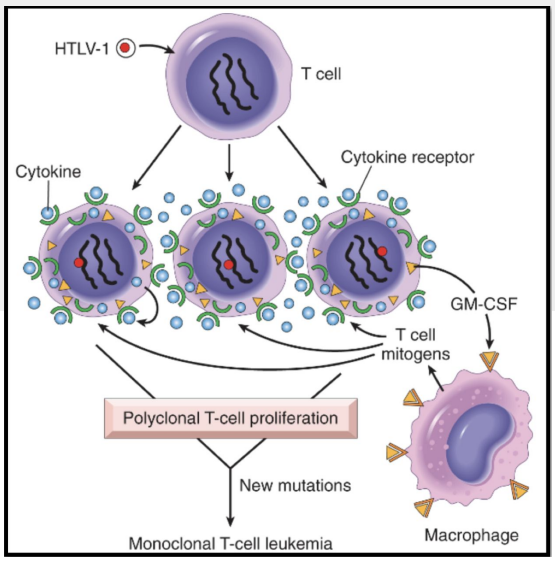
UV rays of sunlight: It causes skin cancers: melanoma, squamous cell carcinoma & basal cell carcinoma. It is capable of DNA damage & mutations of p53 tumor suppressor gene.
When extensive exposure to UV rays occurs, the repair system is overwhelmed causing skin cancer.

Viral & Microbial Oncogenes

Viral & microbial oncogenes include:
- RNA viruses
- DNA viruses
- Other micro-organisms e.g. H. Pylori bacteria

Host cells have endogenous gene to maintain a normal cell cycle.
Oncogene viruses induce cellular proliferation, mimic or block cellular signals necessary for the cell cycle regulation.

RNA oncogenic viruses:
Human T cell lymphotropic virus-1 (HTLV-1), a retrovirus, infects & transforms T-lymphocytes.
It causes T-Cell leukemia/Lymphoma after a prolonged latent period (20-30 years). It is endemic in Japan & the Caribbean.
It is transmitted like HIV but only 1% of infected patients develop T cell leukemia/Lymphoma. No cure or vaccine to HTLV-1 and Treatment: chemotherapy with common relapses.



Viral & Microbial Oncogenes

DNA oncogenic viruses:
DNA viruses form stable associations with hosts DNA, thus the transcribed viral DNA transforms the host cells.
- Human papilloma virus (HPV)
- Epstein Barr virus (EBV)
- Hepatitis B virus (HBV)
- Kaposi sarcoma herpesvirus (KSHV, also called human herpesvirus-8 [HHV-8])

HPV infection: HPV has more than 70 serotypes, It is a sexually transmitted. It causes benign warts, squamous cell carcinoma of the cervix, anogenital region, mouth & larynx.

HPV types 6 and 11 ⟶ Genital warts
HPV types 16, 18, 31 ⟶ 85% of cervical carcinomas are caused by HPV 16 or 18 • High risk HPV types integrates with the host's DNA

The oncogenic potential of HPV 16 and 18 can be related to products of two early viral genes, E6 and E7.
E6 protein binds to Rb tumor suppressor and releases the E2F transcription factors that normally are sequestered by Rb, promoting progression through the cell cycle.
E7 protein binds to p53 & facilitates its degradation

HPV infection alone is not sufficient to cause carcinoma and other factors also contribute to the development of cervical carcinoma e.g. cigarette smoking, coexisting infections, and hormonal changes

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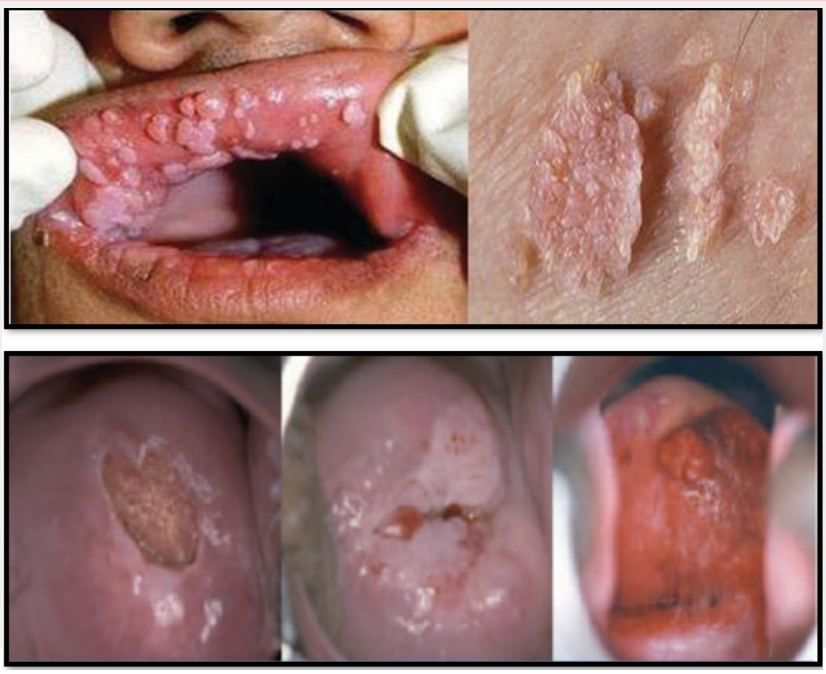


Viral & Microbial Oncogenes

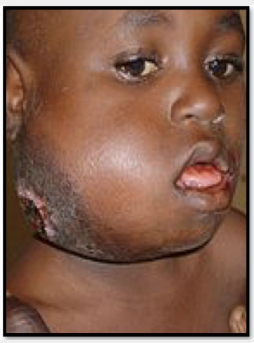
EBV infection: It is a common virus worldwide, It infects B lymphocytes & epithelial cells of the nasopharynx, causing infectious (flu like symptoms) mononucleosis and It several malignant tumors.

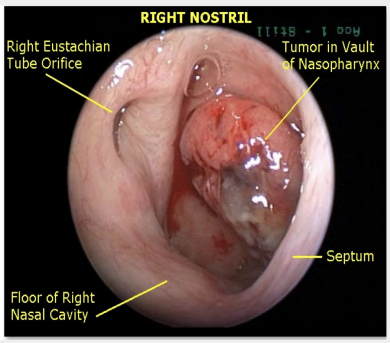
- Burkitt's Lymphoma
- B-cell lymphoma in immunosuppressed
- Nasopharyngeal carcinoma

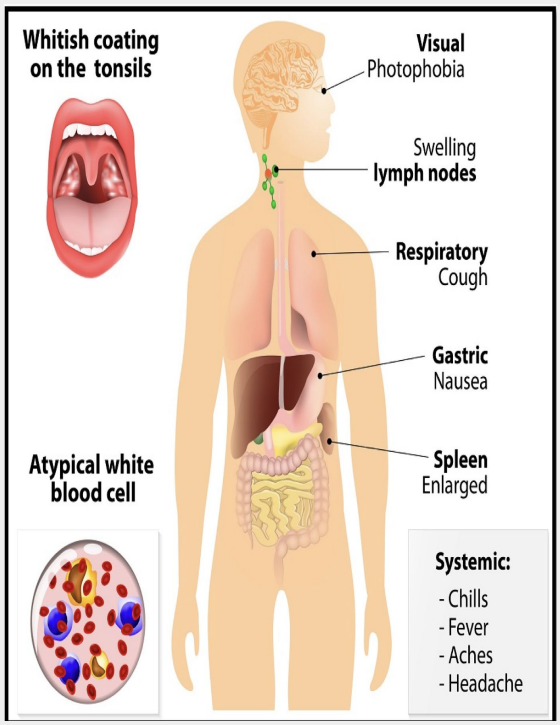
Nasopharyngeal carcinoma is a malignant neoplasm arising from the nasopharyngeal epithelium.
It is endemic in South China and parts of Africa, 100% of cases contain EBV genome in these endemic areas.

Burkitt's lymphoma, a highly malignant B-cell tumor. However, rare sporadic cases occur worldwide. EBV-related Burkitt's lymphoma is the most common childhood tumor in Africa.
All cases have t(8:14) genetic mutation.

B lymphocyte cellular proliferation, It causes loss of growth regulation predisposes the cells to genetic mutations, especially t(8:14).

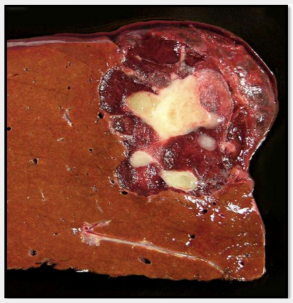


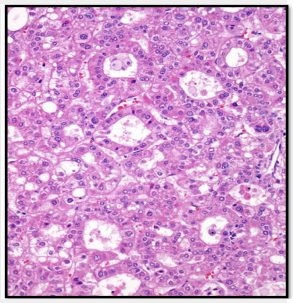




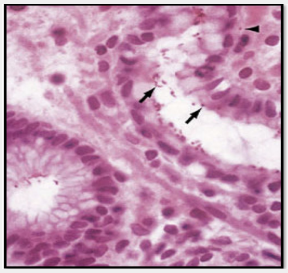
Viral & Microbial Oncogenes

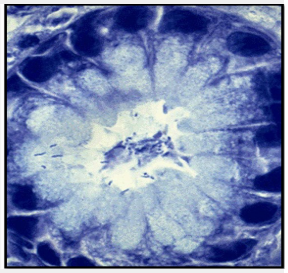
HBV infection: has a strong association with liver cell carcinoma (HCC). It is present world-wide, but most commonly in the far East & Africa. HBV infection incurs up to 200-fold risk of HCC.





Helicobacter Pylori bacteria: It is bacteria that infects the stomach, It causes:
- Peptic ulcers
- Gastric lymphoma " Mucosal Associated Lymphoid Tumor" (MALT)
- Gastric carcinoma

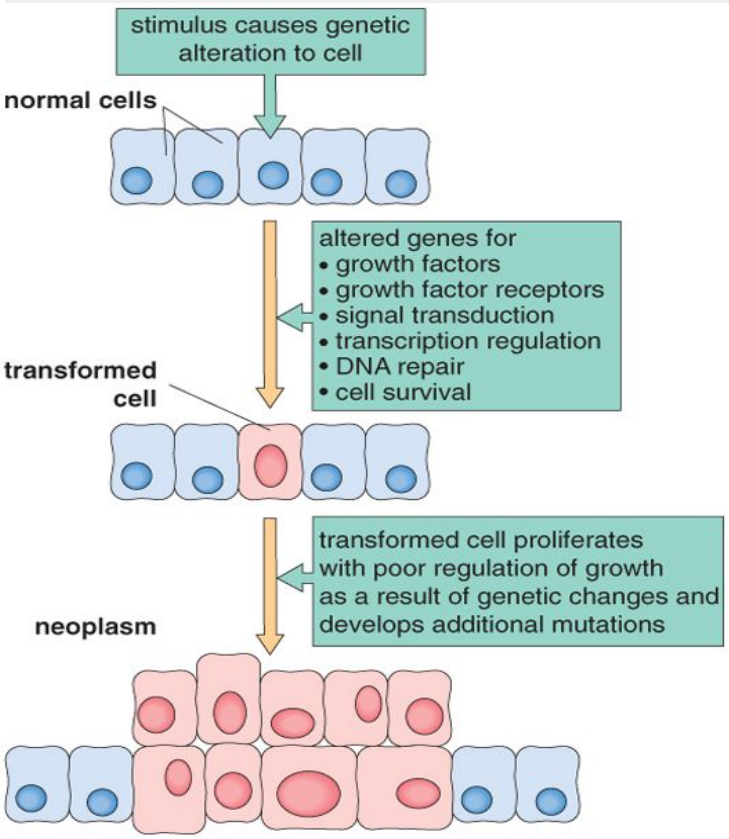


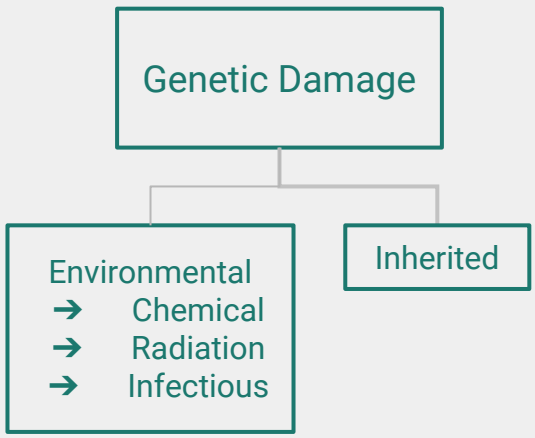


Carcinogenesis

Carcinogenesis is a **multistep** process at both the phenotypic and the genetic levels.

It Starts with Genetic damage → Mutation → single cell which has the genetic damage undergoes neoplastic proliferation → forming the tumor mass.

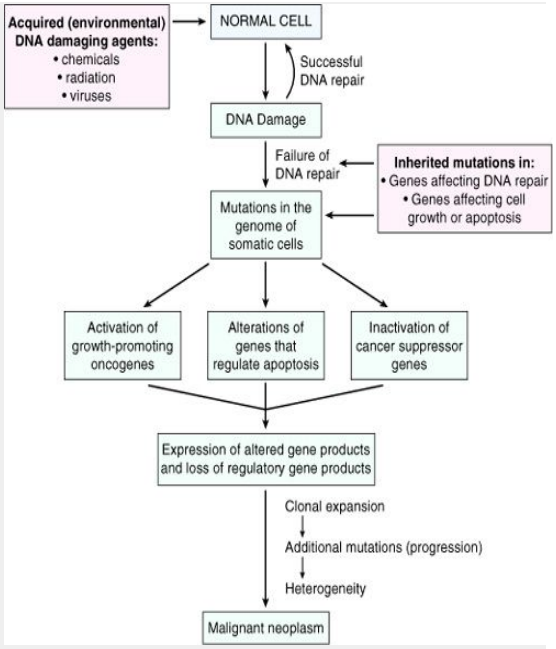




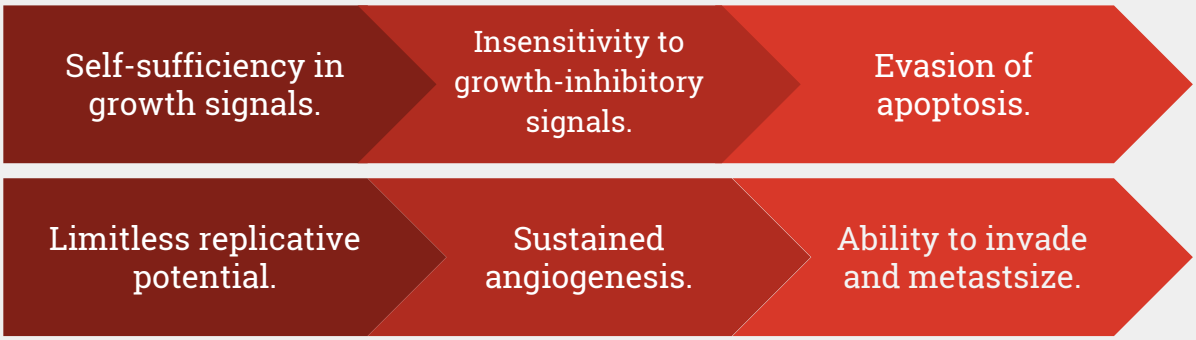
Carcinogenesis

Regulatory genes are the main targets of the genetic damage:

- Growth promoting protooncogenes. Protooncogene > mutation > **oncogene.**
- Growth inhibiting **suppressor** genes
- Genes regulating apoptosis
- DNA repair genes



Main changes in the cell physiology that lead to formation of the malignant phenotype:



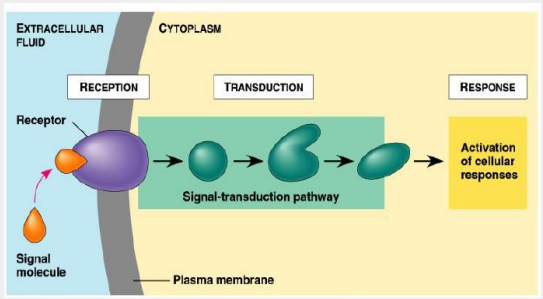
Self-sufficiency in growth signals:

Oncogene: Gene that promote autonomous cell growth in cancer cells. They are derived by mutations in protooncogenes, and characterized by the ability to promote cell growth in the absence of normal growth promoting signals. (causing abnormal cell growth)

Oncoproteins : are the products.

The cell cycle:

1. Binding of a growth factor to its receptor on the cell membrane.
2. Activation of the growth factor receptor leading to activation of signal-transducing proteins.
3. Transmission of the signal to the nucleus
4. Induction of the DNA transcription
5. Entry in the cell cycle and cell division



A)Self-sufficiency in growth signals

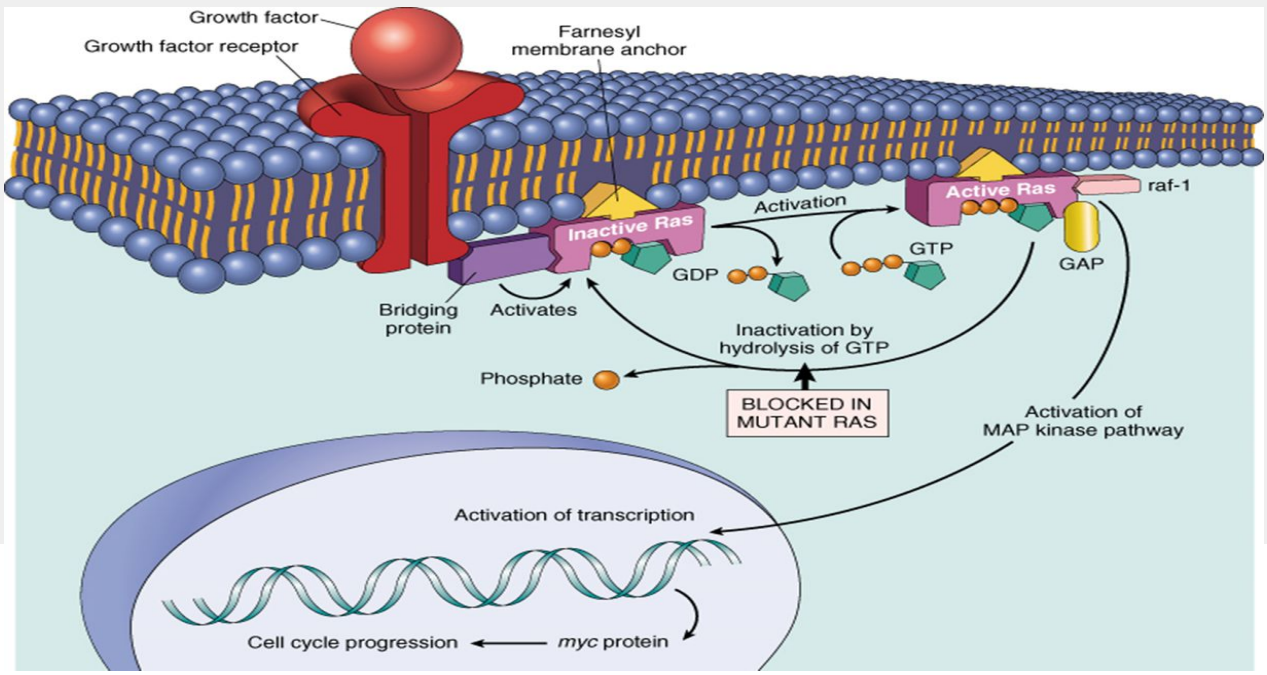
Growth Factors:
Cancer cells are capable to synthesize the same growth factors to which they are responsive.
Sarcomas ⟶ TGF-α
Glioblastoma ⟶ PDGF

Growth Factors Receptors: (two pathways can happens)
1- Receptors ⟶ mutation ⟶ continuous signals to cells and uncontrolled growth.
2- Receptors ⟶ overexpression ⟶ cells become very sensitive hyperresponsive to normal levels of growth factors.

Example:
Epidermal Growth Factor (EGF) Receptor family HER2
Amplified in breast cancers and other tumors, High levels of HER2 in breast cancer indicate poor prognosis.
Anti- HER2 antibodies are used in Treatment. (blocking the receptor)

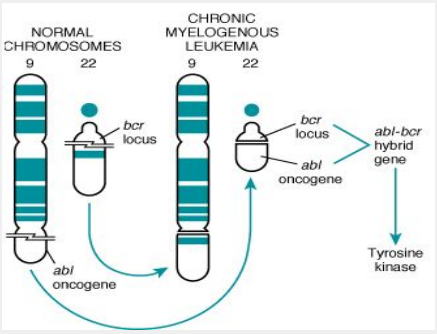
Signal-transducing proteins :
They receive signals from activated growth factors receptors and transmit them to the nucleus. **Examples :** RAS, ABL.

RAS:
30% of all human tumors contain mutated RAS gene. (Colon, Pancreas cancers)
Mutations of the RAS gene is the most common oncogene abnormality in human tumors.
Mutations in RAS ⟶ cells continue to proliferate.



A)Self-sufficiency in growth signals

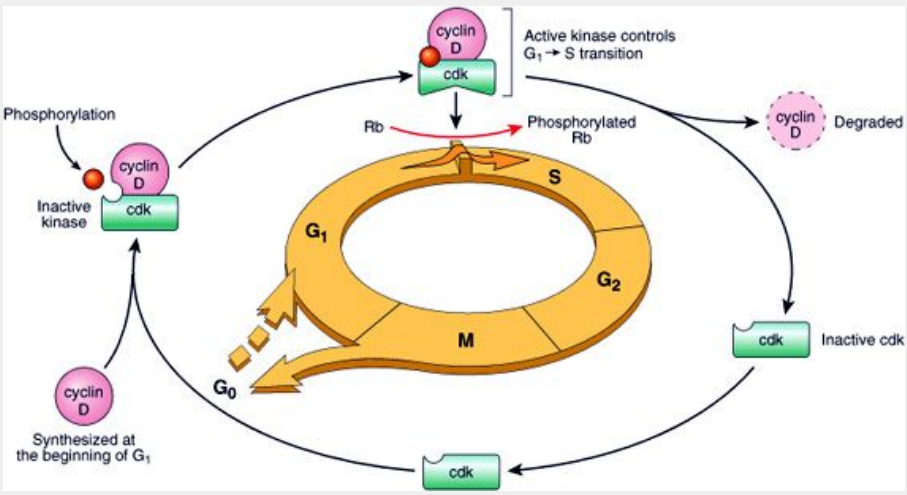
ABL gene:
ABL protooncogene has a tyrosine kinase activity, Its activity is controlled by negative regulatory mechanism.
chronic myeloid leukemia (CML):
t(9,22) ⟶ ABL gene transferred from ch.9 to ch.22
ABL fusse with BCR ⟶ BCR-ABL
BCR-ABL has tyrosine kinase activity (oncogenic).
CML patients are treated with Gleevec which is inhibitor of ABL kinase.



Nuclear transcription factors:
Mutations may affect genes that regulate transcription of DNA ⟶ growth autonomy.
Example: MYC (inside the nucleus)
MYC protooncogene produce MYC protein when cell receives growth signals and then MYC protein binds to DNA leading to activation of growth-related gene.
Normally MYC decrease when cell cycle begins but in tumors there is sustained expression of MYC which continuous proliferation.
Burkitt Lymphoma MYC is dysregulated due to t(8,14).

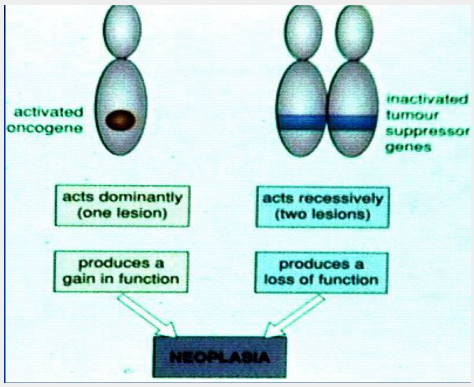
Cyclins and cyclins- dependent kinases (CDKs):
Progression of cells through cell cycles is regulated by CDKs after they are activated by binding with cyclins.
Mutations that dysregulate cyclins and CDKs will lead to cell proliferation.

Cyclin D genes are overexpressed in breast, esophagus and liver cancers.
CDK4 is amplified in melanoma and sarcomas.

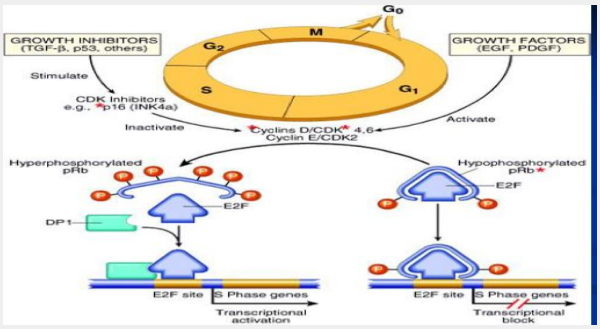


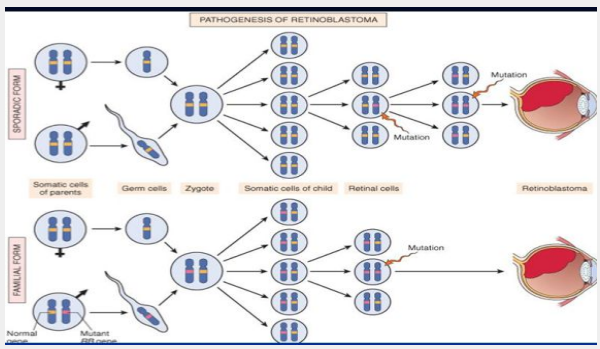
B)Insensitivity to growth-inhibitory signals

Tumor suppressor genes control (apply brakes) cell proliferation
If mutation caused disruption to them ⟶cell becomes insensitive to growth inhibition ⟶ uncontrolled proliferation
Examples: RB, TGF-b, APC, P53



RB (retinoblastoma) gene: First tumor supressor gene discovered. It was discovered initially in retinoblastomas but it is found in other tumors, e.g. breast cancer.
RB gene is a DNA-binding protein and located on chromosome 13
RB gene exists in " active " and " inactive" forms
If active will stop the advancing from G1 to S phase in cell cycle.
If cell is stimulated by growth factors ⟶inactivation of RB gene brake is released⟶cells start cell cycle (G1, S , M) ⟶RB gene is activated again.
Retinoblastoma is an uncommon childhood tumor. Retinoblastoma is either sporadic (60%) (scattered or isolated) or familial (40%) (relating to or occurring in a family or its members)
Two mutations required to produce retinoblastoma. Both normal copies of the gene should be lost to produce retinoblastoma.



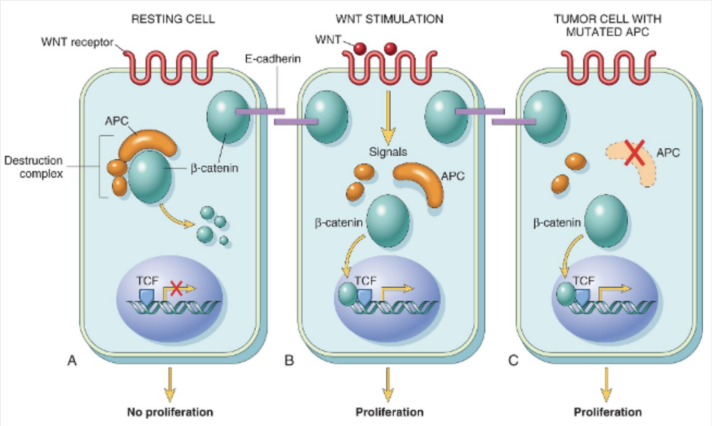


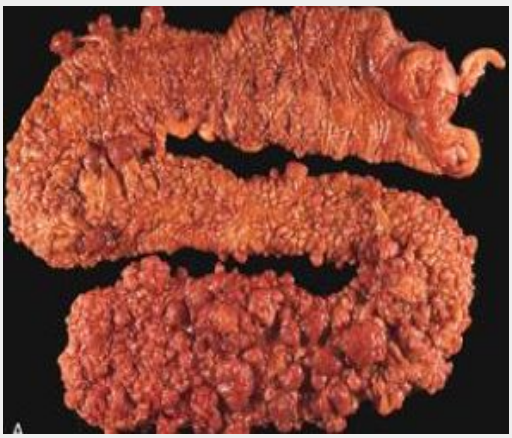
Transforming Growth Factor- b pathway: TGF-b is an inhibitor of proliferation. It regulate RB pathway. Inactivation of TGF-b lead to cell proliferation.

Mutations in TGF-b pathway are present in:
100% of pancreatic cancers
83% of colon cancers

B)Insensitivity to growth-inhibitory signals

Adenomatous Polyposis Coli – b Catenin pathway: APC is tumor suppressor gene. APC gene loss is very common in colon cancers. It has anti-proliferative action through inhibition of beta-Catenin which activate cell proliferation. Individuals with mutant APC develop thousands of colonic polyps. One or more of the polyps will progress to colonic carcinoma.
APC mutations are seen in 70% to 80% of sporadic colon cancers.

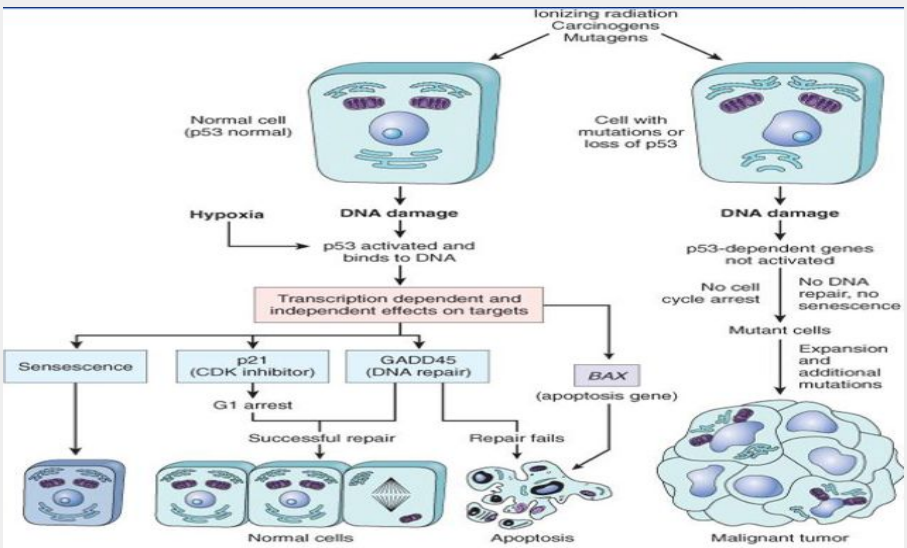




P53: It has multiple functions Mainly:

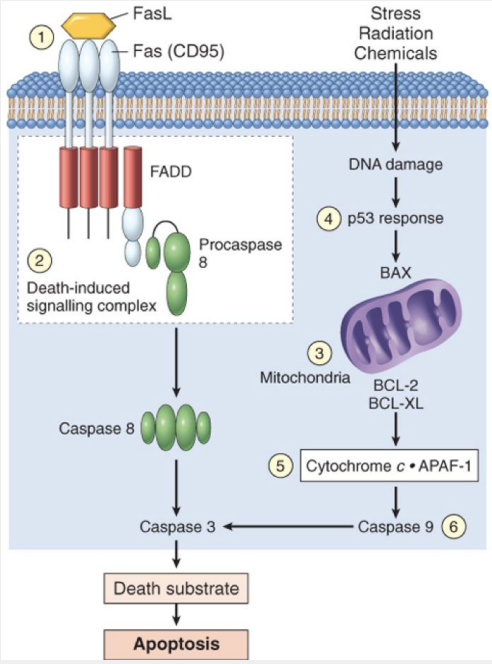
- Tumor suppressor gene (anti-proliferative)
- Regulates apoptosis

P53 senses DNA damage ⟶ Causes G1 arrest to give chance for DNA repair ⟶ Induce DNA repair genes ⟶ If a cell with damaged DNA cannot be repaired, it will be directed by P53 to undergo apoptosis.
<u>With loss of P53</u>, DNA damage goes unrepaired, Mutations will be fixed in the dividing cells, leading to malignant transformation.



C) Evasion of apoptosis

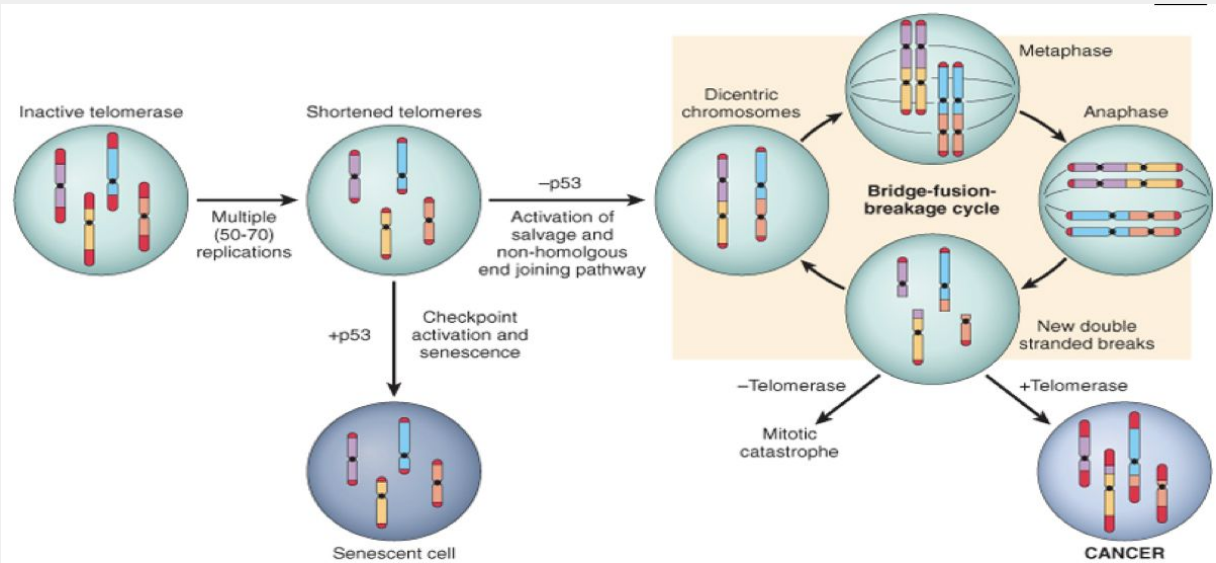
Mutations in the genes regulating apoptosis **are factors in malignant transformation.**
Cell survival is **controlled** by genes that promote and inhibit apoptosis.
Reduced CD95 level inactivate **death–induced signaling cascade** that cleaves DNA to cause death ⟶ tumor cells are less susceptible to apoptosis.
DNA damage induced apoptosis (with the action of P53) can be blocked in tumors.
loss of P53 and up-regulation of BCL2 prevent apoptosis e.g. follicular lymphoma.



D) limitless Replicative potential

Normally there is progressive shortening of telomeres at the ends of chromosomes.
Telomerase is active in normal stem cells but absent in somatic cells.

In tumor cells: activation of the enzyme telomerase, which can maintain normal telomere length.



E) Sustained angiogenesis

Neovascularization has **two main effects**:

- Perfusion supplies oxygen and nutrients
- Newly formed endothelial cells stimulate the growth of adjacent tumor cells by secreting growth factors, e.g **PDGF, IL-1**

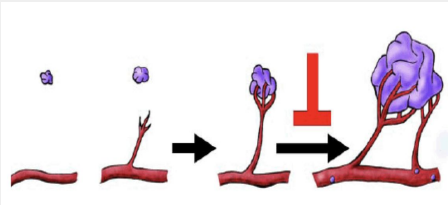
Angiogenesis is required for metastasis.

How do tumors develop a blood supply?

Tumor-associated angiogenic factors, These factors may be produced by tumor cells or by inflammatory cells infiltrating.
the tumor e.g. macrophages.

Important factors :

- Vascular endothelial growth factor (VEGF)
- Fibroblast growth factor

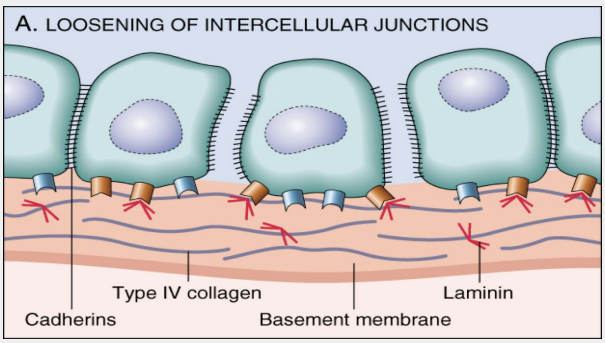


E) Ability to invade and metastsize

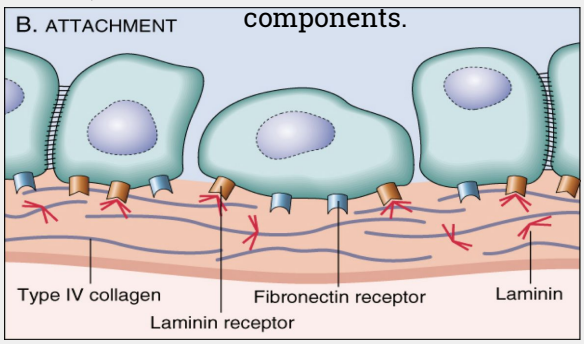
Tow Phases:

1) Invasion of extracellular matrix: (Four Steps):

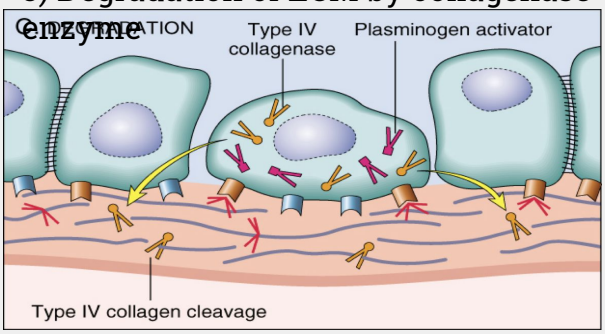
1) Detachment of tumor cells from each other.



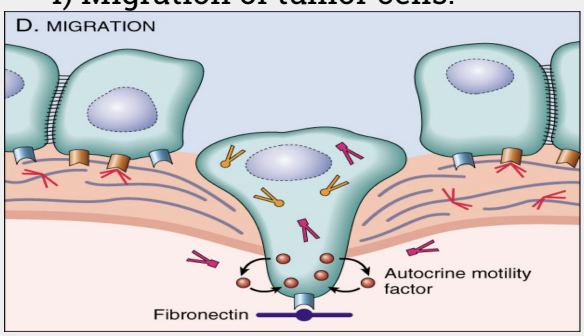
2) Attachments of tumor cells to matrix components.



3) Degradation of ECM by collagenase enzyme



4) Migration of tumor cells.



2) Vascular dissemination and homing of tumor cells:

- May form emboli.
- Most travel as single cells.
- Adhesion to vascular endothelium.
- Extravasation.

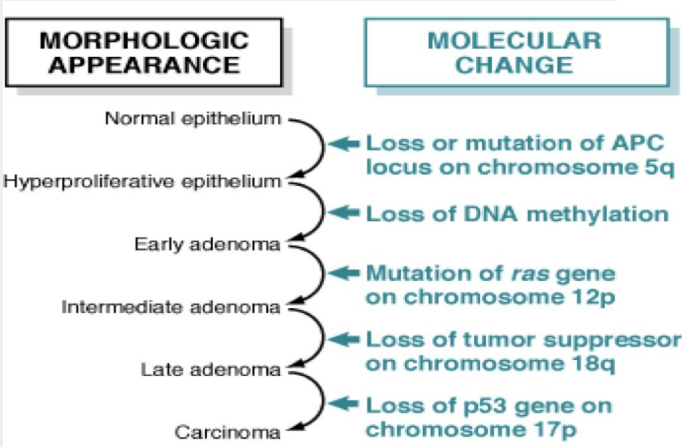
Genomic Instability

Enabler of malignancy due to defect in DNA repair genes.

Examples:

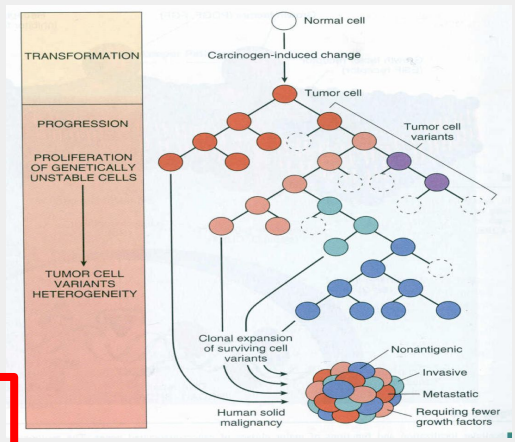
- Hereditary Nonpolyposis colon carcinoma(HNPCC)
- Xeroderma pigmentosum.
- **Familial breast cancer:**
  Due to mutations in BRCA1 and BRCA2 genes, these genes regulate DNA repair, Account for 80% of familial breast cancer They are also involved in other malignancies.

Cancer results from accumulation of multiple mutations.
All cancers have **multiple genetic alterations, involving activation of several oncogenes and loss of two or more tumor suppressor genes.**



Tumor progression

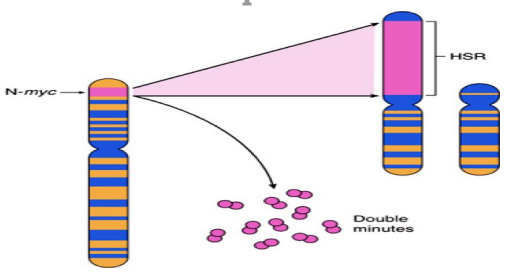
Many tumors become more aggressive and acquire greater malignant potential this is called **tumor progression.**
By the time, the tumor become clinically evident, their constituent cells are extremely heterogeneous.



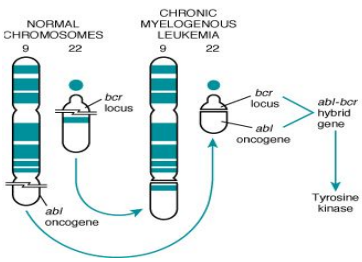
Karyotypic Changes in Tumors

Translocations: - In CML : t(9,22) (Philadelphia chromosome) - In Burkitt Lymphoma : t(8,14) - In Follicular Lymphoma: t(14,18)	**Deletions**	**Gene amplification:** - Breast cancer : HER-2

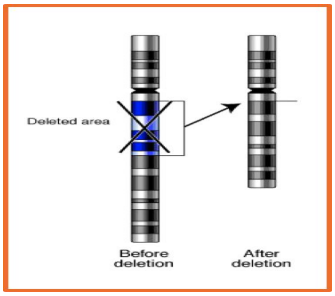
Gene amplification



Translocation



Deletions



Summary -From team 436

Normal function in normal cells	Oncogene	Mutation	Disease	Treatment
Growth factors	TGF-α	Produced in	Sarcomas	
	PDGF	Produced in	Glioblastoma	
Growth factor receptors	HER-2 (from EGF receptor family)	Amplified in	Breast cancer	Anti-HER2 antibodies
Signal transduction proteins	RAS	If mutated cells continue to proliferate	Colon , pancreatic cancers	
	ABL Has tyrosine activity	BCR-ABL Translocation t(9,22) (Philadelphia chromosome)	LMD (chronic myeloid leukemia)	Gleevec
Nuclear transcription factor	MYC	t(8,14) ,mostly by Epstein-Barr virus	Burkitt Lymphoma	
Cell cycle regulation	Cyclins	Cyclin D is amplified in	Breast, osophagus, liver cancer	
	CDKs :Cyclin Dependent Kinases	CDK4 is amplified in	-Melanoma -sarcomas	
Tumor suppressor genes	RB	Located in chromosome 13	- retinoblastoma (two mutations required to produce retinoblastoma) , either familial or sporadic -breast cancer	
	TGF-β	mutated in	-100% all of pancreatic cancer -83% of colon cancer	
	APC : Adenomatous Polyposis Coli	mutated in	-Adenomatous polyposis in colon -colon cancer	
	P53 :regulate DNA repair + cell apoptosis	-acquired in most of cases -inherited: Li-Fraumeni syndrome (autosomal dominant)	Almost ALL types of cancers	
	BRCA1 BRCA2	mutated in	Familial breast cancer	
Evasion of Apoptosis	BCL-2 (apoptosis inhibitor)	t(14:18) =overexpressed BCL2	Follicular Lymphoma	

Tumor Antigen

Tumor Antigens:

- **Tumor-specific antigen**: found only on tumor cells.
- **Tumor-associated antigen** (nonspecific)**:** found on tumor cells and some normal cells.

Classes of tumor antigens:

- **Products of mutated oncogenes and tumor suppressor genes.** P53 tumor suppressor gene, RAS oncogene
- **Products of amplified genes.** HER2-NEU
- **Tumor antigens produced by oncogenic viruses.** HPV, EBV
- **Oncofetal antigens**: expressed during embryogenesis (fetal life) but not in normal adult tissues. CEA in colon and CEA liver carcinomas.
- **Cell type–specific differentiation antigens:** Tumors express molecules that normally are present on the cells of origin. These antigens are called differentiation antigens, because they are specific for particular lineages or differentiation stages of various cell types. PSA in prostatic carcinoma (specific screening)

Host Defense Against Tumors: (Antitumor effector mechanisms)

- Cytotoxic T lymphocytes
- Natural killer cells
- Macrophages

Humoral mechanisms:

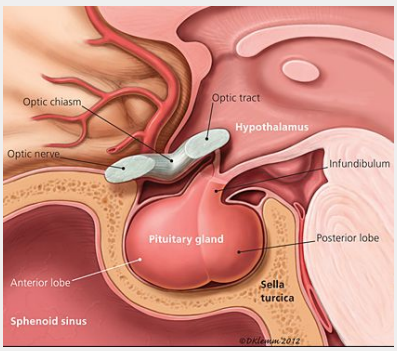
- Complement system
- Antibodies

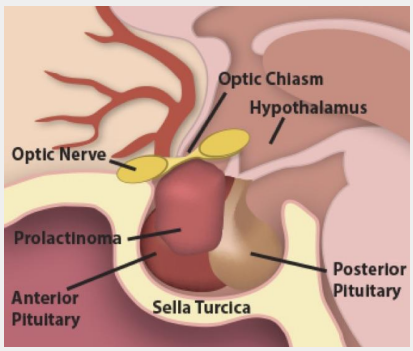
Clinical Aspects of Neoplasia

Both malignant & benign tumors may cause problems because of:
• Location and impingement on adjacent structures
• Bleeding, secondary fractures or infections
• Symptoms that result from rupture, obstruction or infarction
• Functional activity such as hormone synthesis or the development of paraneoplastic syndromes
• Cachexia or wasting.

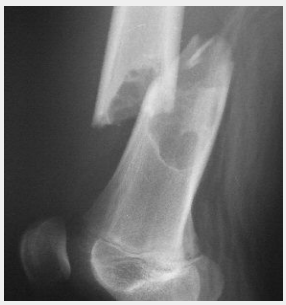
Clinical Aspects of Neoplasia

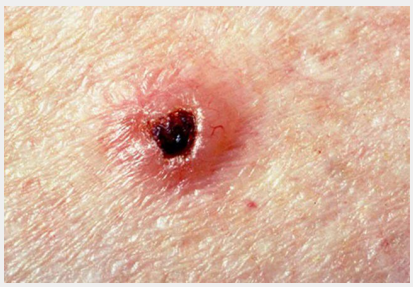
Location and impingement on adjacent structures: it is crucial in both benign and malignant tumors.
A small (1-cm) pituitary adenoma can compress and destroy the surrounding normal gland, giving rise to hypopituitarism. (due to the location benign tumor can cause problems)
A 0.5-cm leiomyoma in the wall of the renal artery may encroach on the blood supply, leading to renal ischemia and hypertension.



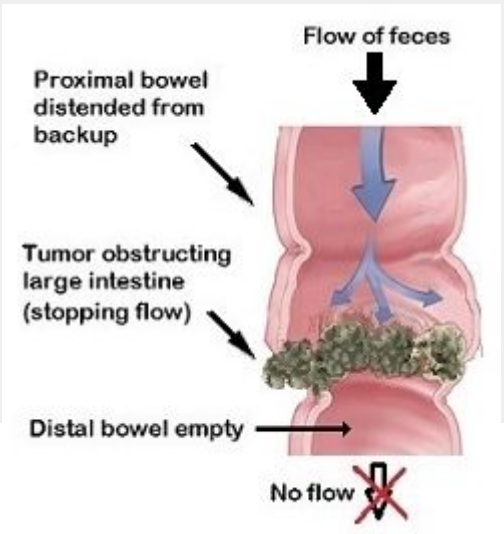


Bleeding, secondary fractures and infections: A tumor may ulcerate through a surface or adjacent structures causing consequent bleeding or secondary infection or fracture.





Symptoms that result from rupture, obstruction or infarction:



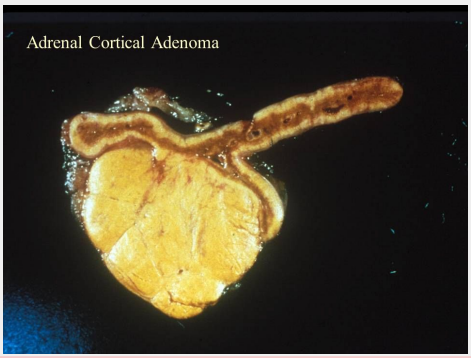
Clinical Aspects of Neoplasia

Functional activity such as hormone synthesis or the development of paraneoplastic syndromes:
Hormone production is seen with benign and malignant neoplasms arising in endocrine glands.

Adenomas and carcinomas arising in the beta cells of the pancreatic islets of Langerhans can produce hyperinsulinism, sometimes fatal.

Some adenomas and carcinomas of the adrenal cortex elaborate corticosteroids that affect the patient (e.g., aldosterone, which induces sodium retention, hypertension, and hypokalemia).

Such hormonal activity is more likely with a well-differentiated benign tumor than with a corresponding carcinoma.



Paraneoplastic syndromes:
They are symptoms that occur in cancer patients & cannot be explained.
- They are diverse and are associated with many different tumors.
- They appear in 10% to 15% of patients.
- They may represent the earliest manifestation of an occult neoplasm.
- They may represent significant clinical problems & may be lethal.
- They may mimic metastatic disease

The most common paraneoplastic syndrome are:
- Hypercalcemia
- Cushing syndrome
- Nonbacterial thrombotic endocarditis

The most often neoplasms associated with these syndromes:
- Lung and breast cancers and hematologic malignancies

Clinical Aspects of Neoplasia

Clinical Syndrome	Major Forms of Neoplasia	Causal Mechanism(s)/Agent(s)
Endocrinopathies		
Cushing syndrome	Small cell carcinoma of lung Pancreatic carcinoma Neural tumors	ACTH or ACTH-like substance
Syndrome of inappropriate anti-diuretic hormone secretion	Small cell carcinoma of lung; intracranial neoplasms	Anti-diuretic hormone or atrial natriuretic hormones
Hypercalcemia	Squamous cell carcinoma of lung Breast carcinoma Renal carcinoma Adult T cell leukemia/lymphoma	Parathyroid hormone–related protein, TGF-α
Hypoglycemia	Fibrosarcoma Other mesenchymal sarcomas Ovarian carcinoma	Insulin or insulin-like substance
Polycythemia	Renal carcinoma Cerebellar hemangioma Hepatocellular carcinoma	Erythropoietin
Nerve and Muscle Syndrome		
Myasthenia	Bronchogenic carcinoma, thymoma	Immunologic
Disorders of the central and peripheral nervous systems	Breast carcinoma, teratoma	Immunologic
Dermatologic Disorders		
Acanthosis nigricans	Gastric carcinoma Lung carcinoma Uterine carcinoma	Immunologic; secretion of epidermal growth factor
Dermatomyositis	Bronchogenic and breast carcinoma	Immunologic
Osseous, Articular, and Soft-Tissue Changes		
Hypertrophic osteoarthropathy and clubbing of the fingers	Bronchogenic carcinoma	Unknown
Vascular and Hematologic Changes		
Venous thrombosis (Trousseau phenomenon)	Pancreatic carcinoma Bronchogenic carcinoma Other cancers	Tumor products (mucins that activate clotting)
Nonbacterial thrombotic endocarditis	Advanced cancers	Hypercoagulability
Anemia	Thymoma	Immunologic
Others		
Nephrotic syndrome	Various cancers	Tumor antigens, immune complexes

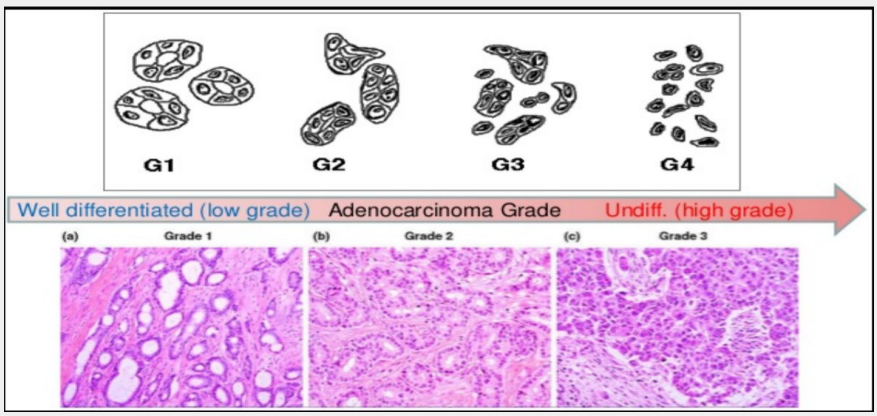
Cancer cachexia (severe weight loss):
It is usually accompanied by weakness, anorexia and anemia. The severity of cachexia is generally correlated with the size and extend of spread of the cancer.

The origin of cancer cachexia is multifactorial:
- Anorexia (reduced calorie intake): TNF suppresses appetite.
- Increased basal metabolic rate & calorie expenditure.
- General metabolic disturbance.

Grading and staging of cancer

Grading: It is based on the cytologic differentiation of tumor cells and the number of mitoses within the tumor.
Malignant tumors are classified as:

- Grade I : well differentiated
- Grade II : moderately differentiated
- Grade III : poorly differentiated
- Grade IV : anaplastic (undifferentiated)



Staging: is based on the size of the primary lesion, its extent of spread to regional lymph nodes, and the presence or absence of metastases.Two methods of staging are currently in use: the TNM system (T,primary tumor; N, regional lymph node involvement; M, metastases) and the AJC (American Joint Committee) system.

TNM staging system:

- T0 (no tumor), Tis, T1, T2, T3, and T4 describe the increasing size of the primary lesion
- N0 (no node involvement) , N1, N2, and N3 indicate progressively advancing node involvement
- M0 (no metastases) and M1 (present of metastases) reflect the absence and presence, respectively, of distant metastases.

Stage	Definition
Tis	In situ, non-invasive (confined to epithelium)
T1	Small, minimally invasive within primary organ site
T2	Larger, more invasive within the primary organ site
T3	Larger and/or invasive beyond margins of primary organ site
T4	Very large and/or very invasive, spread to adjacent organs
N0	No lymph node involvement
N1	Regional lymph node involvement
N2	Extensive regional lymph node involvement
N3	More distant lymph node involvement
M0	No distant metastases
M1	Distant metastases present

Laboratory Diagnosis of Cancer

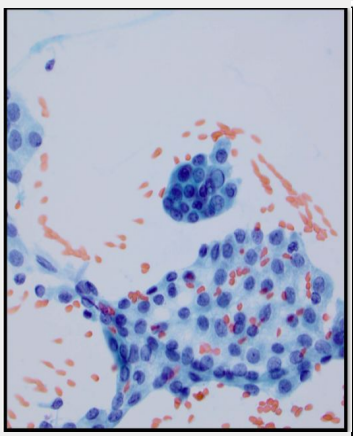
Laboratory diagnosis of cancer can be achieved by:
• Morphologic methods
• Biochemical assays
• Molecular tests

Morphologic methods include microscopic tissue or cellular diagnosis: It is the gold standard for cancer diagnosis.
Several sampling approaches are available:
• Biopsy, excision & frozen section
• Fine-needle aspiration
• Cytologic smears
• Immunohistochemical stains
• Flow cytometry

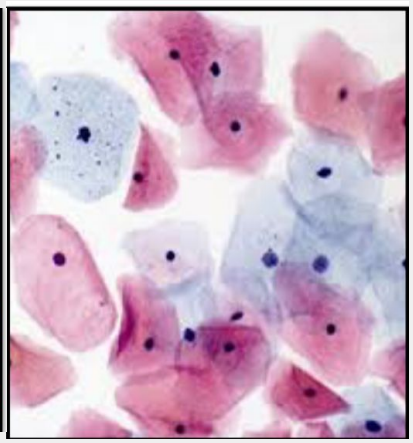
Sampling approaches:
• Biopsies
• Surgical excisions
• Frozen section: a method in which a sample is quick-frozen and sectioned, permits histologic evaluation within minutes.

Laboratory Diagnosis of Cancer:
• Fine needle aspiration: it involves aspiration of cells from a mass, followed by cytologic examination of the smear.
• Cytologic (Papanicolaou) smears provide another method for the detection of cancer. Neoplastic cells are less cohesive than others and are therefore shed into fluids or secretions.

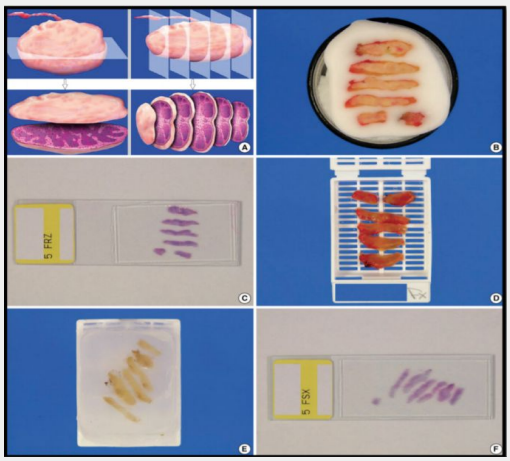
FNA



Pap smear



Frozen Section



Laboratory Diagnosis of Cancer

Immunocytochemistry offers a powerful adjunct to routine histologic examination.
Flow cytometry is used routinely in the classification of leukemias and lymphomas.

Biochemical assays: They are useful for measuring the levels of tumor associated enzymes, hormones, and tumor markers in serum.
They are useful in screening, determining the effectiveness of therapy & detecting tumor recurrences.
Elevated levels may not be diagnostic of cancer e.g. PSA.(not specific)
Only few tumor markers are proven to be clinically useful e.g. CEA & AFP.

Molecular tests:
• Polymerase chain reaction (PCR): PCR is useful for the detection of BCR-ABL transcripts in chronic myeloid leukemia.
• Fluorescent in situ hybridization (FISH)
• FISH is useful for detecting chromosomal translocations characteristic of many tumors.
• Both PCR and FISH can show amplification of oncogenes e.g.HER2-NEU & N-MYC.

DNA microarray analysis:
• It evaluates the expression of thousands of genes.
•Different tissues have different patterns of gene expression.
• It is a powerful tool for subcategorizing diseases e.g. lymphomas.
• It confirms the morphologic diagnoses.
• It is useful in illustrating genes involved in certain disease & help plan possible therapies.

Team leaders

- نجود العبداللطيف
- مهند أحمد

Team members

- إبراهيم الشقراوي
- خالد الخاني
- سهيل باسهيل
- نايف السليس
- طارق العقيل
- حميد الحافظ
- علي آل داوود
- رزان الرباح
- طيف الشمري
- أميرة الزهراني
- لمى الزامل
- لينا النصار

Special thanks to:

Pathology Team 436